NIH Guidelines

The purpose of the National Institutes of Health Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules *(NIH Guidelines April 2019)* is to specify the practices for constructing and handling: (i) recombinant nucleic acid molecules, (ii) synthetic nucleic acid molecules, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules, and (iii) cells, organisms, and viruses containing such molecules.

Recombinant and synthetic nucleic acid molecules are defined as:

1) molecules that a) are constructed by joining nucleic acid molecules and b) that can replicate in a living cell; or
2) nucleic acid molecules that are chemically or by other means synthesized or amplified, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules (i.e. synthetic nucleic acids); or
3) molecules that result from the replication of those described in 1 or 2 above.

The *NIH Guidelines* also cover risk assessment for various types of organisms that may be source, vector or host for recombinant and synthetic nucleic acid molecules including:

1) Pathogens

A pathogen or infectious agent is any agent associated with disease in healthy human adults. There are four Risk Groups (RGs) discussed in the *NIH Guidelines* which generally correlate with the Biosafety Levels (BSL) described in the CDC publication "*Biosafety in Microbiological and Biomedical Laboratories* (BMBL)." Agents in RG2/BSL2 or higher are considered human pathogens.

2) Biohazards

Biohazards are infectious agents or hazardous biological materials that present a risk or potential risk to the health of humans, animals, or the environment. The risk can be direct through infection or indirect through damage to the environment. Biohazardous materials include certain types of recombinant DNA; organisms and viruses infectious to humans, animals or plants (e.g. parasites, viruses, bacteria, fungi, prions, rickettsia); and biologically active agents (i.e. toxins, allergens, venoms) that may cause disease in other living organisms or cause significant impact to the environment or community.

Any nucleic acid molecule experiment, which according to the *NIH Guidelines* requires approval by NIH, must be submitted to NIH or to another Federal agency that has jurisdiction for review and approval. When experiments involve the deliberate transfer of recombinant or synthetic nucleic acid molecules, or DNA or RNA derived from recombinant or synthetic nucleic acid molecules, into human research participants (human gene transfer), no research participant shall be enrolled until Institutional Biosafety Committee (IBC) approval (from the clinical trial site) has been obtained; Institutional Review Board (IRB) approval has been obtained; and all applicable regulatory authorization(s) have been obtained.

Assessment of Human Gene Therapy Trials

In April 2019, the NIH streamlined individual human gene transfer (HGT) protocol reporting requirements, however it is important to note that robust oversight over HGT research will continue through both Federal and local oversight bodies.

When conducted by an entity subject to the *NIH Guidelines* (see Section I-C), HGT research (see Section III-C) is covered under the NIH Guidelines, as protocols must still be reviewed and approved by Institutional Biosafety Committees to assess biosafety considerations at the clinical trial site. In addition, all other applicable institutional and regulatory authorization(s) and approvals must be obtained before any research with human participants can be initiated.

It is important to note that while NIH has streamlined individual HGT protocol reporting requirements, robust oversight over HGT research will continue through both Federal and local oversight bodies. HGT research remains subject to Food and Drug Administration oversight. In addition, as with all NIH-supported research, HGT research will remain subject to NIH oversight, as well as applicable policies and regulations for the protection of human subjects in research—such as the Common Rule and the NIH policy on Certificates of Confidentiality—and rigorous local oversight will continue to be provided by Institutional Review Boards and Institutional Biosafety Committees.

Institutional Biosafety Committee

The *NIH Guidelines* are applicable to all recombinant and synthetic nucleic acid research that is conducted at or sponsored by an institution that receives any support for recombinant or nucleic acid research from NIH. All non-NIH funded projects involving recombinant or synthetic nucleic acid molecules conducted at or sponsored by an institution that receives NIH funds for projects involving such techniques must comply with the *NIH Guidelines*.

In compliance with the *NIH Guidelines*, Stanley Manne Children's Research Institute affiliated with Ann & Robert H. Lurie Children's Hospital of Chicago has established an Institutional Biosafety Committee (IBC) which is responsible for the local review and oversight of all research utilizing recombinant and synthetic nucleic acid molecules.

The *NIH Guidelines* detail safety practices and containment procedures for clinical research involving recombinant and synthetic nucleic acid molecules, including the creation and use of organisms and viruses containing these molecules. The IBC considers a number of matters including containment levels, facilities, institutional procedures and practices, training and expertise of personnel. The Stanley Manne Children's Research Institute is equipped for Biosafety Level 1 and 2 experiments (BSL1 & BSL2).

The *NIH Guidelines* are intended to assist the IBC and principal investigators in determining safeguards prior to conducting experiments involving recombinant DNA. It is the responsibility of the individual conducting such experiments to ensure that safe practices are followed by adhering to the *NIH Guidelines* and internal policies and procedures, with assistance from the IBC.

IBC Convening Authority and Composition

The Lurie Children's IBC shall include no fewer than five members selected to collectively have experience and expertise in recombinant and synthetic nucleic acid research, the capability to assess the safety of recombinant and synthetic nucleic acid molecules and infectious and biohazardous agents, and the ability to identify any potential risk to public health or the environment. At least two members represent the interest of the surrounding community with respect to health and protection of the environment and shall not be affiliated with Lurie Children's. At least one scientist with expertise in animal containment principles is required when research involves use of recombinant or synthetic nucleic acid molecules or biohazardous agents in animals. At least one plant expert is needed if research involves plants containing recombinant or synthetic nucleic acid molecules, plant-associated microorganisms, or plant-associated small animals are conducted. At least one member shall be a person from laboratory technical staff. At least one person with expertise in vector biology and human gene transfer is needed to serve as member or consultant.

The Chief Research Officer appoints the Chair of the IBC. The Chair of the IBC, in consultation with Research Leadership, selects and appoints the Vice Chair and other committee members. Membership is renewable annually upon mutual agreement of the Chair and the committee member(s).

The Chair shall preside over the IBC meetings and act as liaison between the academic community and the IBC. The Vice Chair performs all the duties of the Chair in the Chair's absence and other such duties as may be assigned.

The Chair shall review all instances of noncompliance and present them to the IBC at a convened meeting for appropriate corrective action, which may include suspension of the registration for possession and/or use of recombinant or synthetic nucleic acid molecules or biohazardous materials. The Chair communicates with and works closely with the Institutional Official and the Director of the Office of Research Integrity and Compliance to evaluate complaints or findings of non-compliance.

To help prepare for their position on the committee, IBC members are required to complete introductory training conducted by the IBC Chair, which includes an overview of the *NIH Guidelines.*

The IBC is registered with the National Institutes of Health Office Science Policy (NIH OSP) and provides NIH OSP with an updated list of IBC members annually, the role of each member, and the biosketch for each member. The NIH OSP considers IBCs as key partners in efforts to ensure that institutions and their research personnel employ procedures and practices that conform to the *NIH Guidelines*. The expertise of IBC members, as well as their knowledge of applicable environmental health and safety practices, is critical to achieving this goal. More information is available at https://ibc-rms.od.nih.gov/Contents/IBC_HOME.aspx

IBC Meetings

The IBC typically meets monthly, but may meet more or less frequently as necessary to implement the *NIH Guidelines*. The IBC meeting dates may be found on Lurie Children's IBC resources page. The IBC Chair may call an emergency meeting of the IBC as necessary to address noncompliance or serious and/or unexpected events.

Prior to any regular meeting, each member shall be sent a copy of all the documents to be discussed at the meeting including, but not limited to IBC registration forms, modifications, inactivations, agenda and minutes, and other documents to be reviewed at the meeting.

Quorum needed to conduct business of the IBC shall consist of a simple majority of members (>50%). The approval or disapproval of registration or suspension of the registration for possession and/or use of recombinant or synthetic nucleic acid molecules or biohazardous agents due to non-compliance requires a majority vote of IBC members present and voting. All members of the IBC except ex-officio members shall have voting rights.

Per institutional policy, IBC members who have a conflict of interest in a project being discussed at the meeting (e.g., are acting as a research investigator, have financial interest in the project, etc.) shall not be present during the IBC's initial or continuing review deliberations and voting.

Minutes of IBC meetings shall include, but not be limited to, the following information:

- Attendance of members and guests;
- IBC actions taken on each registration reviewed and if the registration requires modifications for IBC approval;
- Notation of members who were not present during deliberations and voting on projects with which they have a conflict of interest.

The IBC retains all records for at least three (3) years after completion of the research/project.

IBC Responsibilities

- Review and approve, approve with modifications, table or disapprove Biosafety Registrations for Clinical Research that involves recombinant and synthetic nucleic acid molecules, pathogens, and/or select agents including a full risk assessment, selection of proper containment and any required special provisions. Neither the Chief Research Officer nor any other institutional official may approve any protocol which the IBC has disapproved. However, the Chief Research Officer or their designee may disapprove any protocol which the IBC has approved. Such disapproval may not be appealed and is final.
- Conduct an independent assessment of the containment levels recommended by the PI, as well as those required by the *NIH Guidelines* for any proposed research involving recombinant and synthetic nucleic acid molecules – and – may lower or raise containment within what is allowed by the *NIH Guidelines* based on the risk assessment.
- Conduct an assessment of the facilities, procedures, practices, training and expertise of personnel involved in clinical research with recombinant and synthetic nucleic acids and/or biohazardous agents.
- Where applicable, ensure that all required approvals under the *NIH Guidelines* have been obtained from NIH/OBA prior to initiation of recombinant and synthetic nucleic acid research.

- Review Amendments to previously approved registrations.
- Conduct a periodic review of protocols when a PI plans to continue activity described in the Biosafety Registration for Clinical Research beyond the initial approval period. Notify investigators in writing of the results of the review and the IBC decisions.
- Adopt emergency plans for spill or exposure.
- Report any significant problems with or violations of the *NIH Guidelines* or any significant accidents or illnesses to the Institutional Official and NIH OSP within 30 days. Significant violations or incidents may include items such as:
    - Breach of containment for recombinant and synthetic nucleic acid molecules such as escaped microorganisms, or a spill, outside of containment (i.e.: Biological Safety Cabinet) that cannot be easily and quickly cleaned up by one person.
    - Any illness likely caused by exposure to recombinant and synthetic nucleic acid molecules and biohazards.
    - Willful violation of protocols or conduct of work without prior IBC approval.
- Review policies and procedures pertaining to recombinant and synthetic nucleic acid research and present such for final approval by the Chief Research Officer of the research institute.
- Record all IBC actions and meeting minutes which will be made available for public inspection upon request.
- Conduct periodic inspections of laboratories/facilities engaged in recombinant and synthetic nucleic acid clinical research to ensure standards are followed.
- Ensure that all IBC members are adequately trained in state and federal regulations, and institutional policies and standard operating procedures necessary to reasonably evaluate Biosafety Registrations for Clinical Research.
- Establish a subcommittee or ad hoc committee as necessary to carry out its overall responsibilities.
- For human gene transfer experiments, where the Lurie Children's Hospital is the principal sponsoring institution (and not just a clinical trial site), the IBC is also responsible for ensuring that all aspects of Appendix M of the *NIH Guidelines* (requirements for human gene transfer experiments) have been addressed by the PI, and projects are conducted in compliance with the Lurie Children's health surveillance, and data and adverse event reporting requirements.
- Section III of the *NIH Guidelines* covers the different types of recombinant and synthetic nucleic acid research and the levels of review required for each, ranging from exempt to full review by the IBC depending on the safety risk posed. At Lurie Children's, ALL recombinant and synthetic nucleic acid research must be reviewed by the IBC even if it is "exempt" to ensure the correct status.

Compliance Oversight and Reporting

The IBC has authority to address non-compliance with the Biosafety Registrations or the *NIH Guidelines* in consult with the Institutional Official and the Director of the Office of Research Integrity and Compliance.

The IBC shall take any actions, including suspending an activity or revoking approval of a Biosafety Registration, that are in the committee's judgment necessary, to ensure compliance with applicable federal, state, or local policies, procedures, and regulations. The IBC may take appropriate action in instances where, in its judgment, personnel, property or the community may be endangered.

Non-compliance can result in the IBC taking one or more of the following actions:

- Suspending use of recombinant and synthetic nucleic acid molecules including pathogens and biohazardous materials used in nucleic acid research;
- Termination of the IBC Biosafety Registration;
- Confiscation of the biohazardous material;
- Destruction of the biohazardous material;
- Any other action necessary to protect the public and/or the Lurie Children's

In consultation with the Institutional Official (IO), the Chair or their designee has the authority to close any laboratory in which a required safety procedure is violated. Such action and the safety violations shall be reported immediately to the IBC and the Chief Research Officer of the research institute. The IO does not have the authority to approve a program, project or activity denied by the IBC.

The *NIH Guidelines* require that any significant problems, violations, or any significant research-related accidents and illnesses" be reported to OSP within 30 days. Appendix G of the *NIH Guidelines* specifies certain types of accidents that must be reported on a more expedited basis. Specifically, Appendix G-II-B-2-k requires that spills and accidents in BL2 laboratories resulting in an overt exposure must be immediately reported to the OSP (as well as the IBC). In addition, Appendices G-II-C-2-q and G-II-D-2-k require that spills or accidents occurring in high containment (BL3 or BL4) laboratories resulting in an overt or potential exposure must be immediately reported to OSP (as well as the IBC and BSO).

- Incident Reporting FAQs – May 2019Incident Reporting Template – April 2019

Principal Investigator (PI) Responsibilities

- Submit a completed Clinical Biosafety Registration application for all activities involving recombinant and synthetic nucleic acid and biohazardous materials to the IBC for review and approval;
- Receive written approval of the Biosafety Registration for Clinical Research from the IBC prior to acquiring or working with recombinant and synthetic nucleic acid molecules and/or and biohazardous materials;
- Keep Biosafety Registrations up-to-date by submitting modification requests and continuing reviews in a timely manner;

- Comply with all federal requirements and state requirements when conducting clinical research involving biohazardous materials and with the *NIH Guidelines* when conducting clinical research with recombinant and synthetic nucleic acid.
- Ensure all reporting requirements under the *NIH Guidelines* involving recombinant and synthetic nucleic acid molecules are fulfilled;
- Adhere to IBC approved emergency plans for handling accidental spills and personnel contamination;
- Report immediately any significant problems related to the use of biohazardous materials or any significant research-related accidents and illnesses to Northwestern Memorial Physician Group (NMPG) Corporate Health, the IBC and any other Institutional Committee that has reviewed and approved the research activity;
- Review applicable safety guidelines, procedures, letters of support, and requirements related to the biohazardous materials involved in the research activity;
- Develop standard operating procedures incorporating biosafety procedures or a biosafety manual prepared specifically for the protocol describing the potential biohazards and the precautions to be taken (e.g., hazards and risks, immunizations, personal protective equipment required, decontamination, storage and disposal, spill procedures).;
- Train all project personnel in the safe handling and administration of biohazardous material; at minimum, this means ensuring that all personnel have been informed of any potential health risks and have completed required training before accessing biohazardous material and providing additional training as necessary for procedural or policy changes;
- Limit access to personnel who are involved in the project, have been advised on the potential hazards and properly trained on use of protective clothing and other precautions to prevent exposures, and the exposure evaluation procedures;
- Supervise the safety performance of research personnel and staff to ensure that the required safety practices and techniques are employed;
- Investigate and report any significant problems pertaining to the operating and implementation of containment practices and procedures in writing to the IO, IBC, NIHOSP, and/or other appropriate regulatory authorities.
- Correct work errors and conditions that may result in the release of biohazardous materials;
- Ensure the integrity of the biological and physical containment (biosafety level);
- Ensure the security of biohazardous materials at all times.

Biosafety Registration Process

Principal Investigators intending to utilize recombinant and synthetic nucleic acid molecules, as described in the *NIH Guidelines*, are required to submit a Biosafety Registration for Clinical Research Document to the IBC for review and approval. IBC approval of the Biosafety

Registration for Clinical Research is valid for five (5) years. At expiration, a new Biosafety Registration Document for Clinical Research, Safety Protocol, and all applicable supporting documents must be submitted to the IBC for review and approval to continue clinical research involving recombinant and synthetic nucleic acid molecules and/or biohazardous agents.

The following are experiments covered by the *NIH Guidelines:*

There are six categories of experiments involving recombinant or synthetic nucleic acid molecules:

(i) those that require NIH Director Approval and Institutional Biosafety Committee approval before initiation (see *NIH Guidelines* Section III-A)

(ii) those that require NIH Office of Science Policy (OSP) and Institutional Biosafety Committee approval before initiation (see *NIH Guidelines* Section III-B)

(iii) those that require Institutional Biosafety Committee and Institutional Review Board approvals before initiation and research participant enrollment (see *NIH Guidelines* Section III-C) *e.g. human gene transfer*.

(iv) those that require Institutional Biosafety Committee approval before initiation (see *NIH Guidelines* Section III-D),

(v) those that require IBC notification simultaneous with initiation (see *NIH Guidelines* Section III-E), and

(vi) those that are exempt from the *NIH Guidelines* (see *NIH Guidelines* Section III-F).

If an experiment falls into Section III-A, III-B, or III-C and one of the other Sections as well, the rules pertaining to Section III-A, III-B, III-C shall be followed. If an experiment falls into Section III-F alone, or into Section III-F and into Section III-D or III-E as well, the experiment is considered exempt from the NIH guidelines.

Amendments

If the PI wishes to make modifications to an approved Biosafety Registration for Clinical Research Document, an amendment request must be submitted to the IBC for review and approval. Amendments include, but are not limited to, modification of biohazardous materials, updated Investigator's Brochure, changes in research procedures, or changes that change the risk of the project and/or the biosafety level.

Modifications to research conducted under Sections III-A, III-B, III-C, and III-D must be approved prior to implementing new procedures. The PI must submit an Amendment Request Form and any applicable supporting documents. The IBC may request the additional submission of a signed, dated revised Biosafety Registration for Clinical Research Document when the amendment involves substantive changes to the construction, handling and/or use of recombinant or synthetic nucleic acids; or changes that modify the risk category or biosafety level of agents used in the study. The IBC must be notified of modifications under Section III-E at the time they are implemented.

Notification of modifications to exempt research conducted under Section III-F is not required.

The IBC Personnel Change Form must be submitted for modifications to approved registrations involving a change in personnel only. The Chair of the IBC, acting on behalf of

the Committee, may review and approve amendments that do not require safety review. The IBC will be notified of these administratively approved amendments when they are reported during the next convened IBC meeting.

Inactivations

The IBC Coordinator will send out expiration reminder emails to the Principal Investigator prior to expiration. A final expiration notice will be sent on the date of expiration, informing the PI that all study activity must cease immediately until IBC approval has been obtained. If at that time the PI wishes to obtain IBC approval, a new Biosafety Registration for Clinical Research Document, Safety Protocol, and all applicable supporting documents must be submitted and reviewed by the convened committee. If the PI wishes to inactivate the protocol, an Inactivation form must be submitted.

The Chair of the IBC, acting on behalf of the Committee, may review and approve protocol Inactivations upon completion of appropriate form. The Chair of the IBC, acting on behalf of the Committee, may administratively inactivate protocols after the date of expiration with no response from the study team. The IBC will be notified of these administratively approved inactivations when they are reported during the next convened IBC meeting.